The Journal of Immunology

In This Issue

J Immunol 2012; 188:4125-4126; ;
doi: 10.4049/jimmunol.1290015
http://www.jimmunol.org/content/188/9/4125

Supplementary Material **http://www.jimmunol.org/content/suppl/2012/04/23/188.9.4125.DC1**

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

THE JOURNAL OF IMMUNOLOGY

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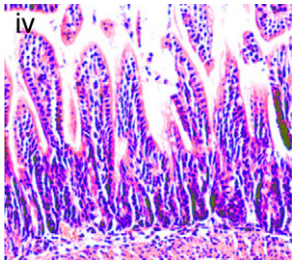
Ending Enterocolitis with Hsp70



Necrotizing enterocolitis (NEC) is a condition in which excessive TLR4 signaling in enterocytes lining the intestines of newborns, particularly premature infants, can cause severe gastrointestinal morbidity and mortality. Afrazi et al. (p. 4543) now show that induction of heat shock protein-70 (Hsp70) expression in enterocytes can limit TLR4 signaling and the development of NEC. Hsp70 is upregulated in response to intracellular stress. Hsp70 induction in enterocytes prior to LPS treatment significantly reduced TLR4-mediated responses, including NF-κB activation, proinflammatory cytokine production, and enterocyte apoptosis, relative to LPS treatment alone. Further analysis revealed that Hsp70 could interact with TLR4 via an EEVD domain in the C-terminus, which promoted ubiquitination and degradation of TLR4 through an interaction with a cochaperone, CHIP. In a murine model of NEC, induction of Hsp70 by genetic or pharmacological strategies curbed TLR4 signaling in the intestinal epithelium and resulted in less severe NEC symptoms. Overall, these results affirm a role for TLR4 signaling in NEC and suggest that induction of proteins like Hsp70 may be a strategy by which NEC can be treated in infants.

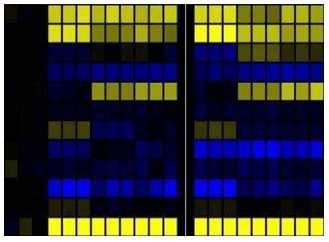
Healing and Resolving

Resolution of inflammation is facilitated in part by lipid mediators, which contribute to wound healing and maintenance of tissue integrity. Oh et al. (p. 4527) now describe how resolvin E2 (RvE2), a lipid mediator derived from eicosapentaenoic acid, is involved in the initiation and resolution of inflammation. In a model of acute inflammation and its resolution, RvE2 and its precursor, 18-HEPE, increased rapidly and then fell gradually over 24 hours in the peritoneal exudates of mice challenged with zymosan. This pattern was different from that of resolvin E1 (RvE1), which is known to peak during the resolution phase. Similar to RvE1, RvE2 was able to stop chemotaxis of human neutrophils in vitro. RvE2 could also enhance the phagocytic function and IL-10 production of human PBMC-derived macrophages. Further analysis revealed an overlap in binding specificity to some G protein-coupled receptors used by both RvE1 and RvE2. In addition, RvE2 was detected in healthy human plasma, and treatment of human blood with RvE2 could downregulate surface expression of the integrin CD18 on both macrophages and neutrophils. These results better define the anti-inflammatory and proresolving functions of RvE2 and highlight the pleiotropic activities of resolvins during inflammation.

Potent Double Positives

Mounting evidence indicates that $CD4^+CD8^+$ double positive (DP) T cells are not only found in the thymus, but can also be detected in peripheral blood of humans and other animals. Frahm et al (p. 4289) have characterized the proliferative capacity and functionality of DP T cells in individuals infected with HIV. DP T cells from acutely infected HIV^+ patients underwent significantly greater proliferation in response to in vitro HIV peptide stimulation relative to $CD4^+$ or $CD8^+$ T cells. HIV-specific DP T cells also showed greater multifunctionality than $CD4^+$ or $CD8^+$ T cells from acutely infected individuals, defined by expression of three or more of the molecules CD107a, IFN-γ, IL-2, MIP-1β, or perforin. DP T cells did not show any significant Ag-specific differences with respect to proliferation. In contrast, multifunctional DP T cells responded most strongly to a peptide pool specific for the HIV proteins VPR, VPU, Nef, Rev, and Tat. Proliferating or multifunctional DP T cells from a cohort of chronically infected HIV controllers generated responses to a pool of peptides specific to Gag as well as to the VPR, VPU, Nef, Rev, and Tat peptide pool. These data suggest that DP T cells can mount a robust and diverse response to HIV during acute infection. Future studies are needed to determine how this subset affects viral replication and disease progression.

Dose Drives Apoptosis

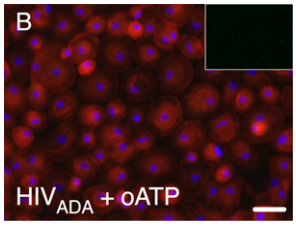


The generation of an Ag-specific $CD8^+$ T cell response involves the rapid expansion and differentiation of naive T cells. The majority of T cells are cleared by apoptosis during the subsequent contraction phase, and some of the surviving T cells develop into memory T cells. Wensveen et al. (p. 4256) describe how costimulation via CD27 and CD70 promotes apoptosis and shapes memory $CD8^+$ T cell responses in an Ag dose-dependant manner. In vitro stimulation with a low Ag dose enhanced CD27-expressing $CD8^+$ T cell proliferation and survival in the presence of APCs expressing the CD27 ligand, CD70, compared with APCs lacking CD70. In contrast, stimulation with a high dose of Ag in combination with CD27/CD70 costimulation resulted in greater Fas-mediated Ag-specific T cell apoptosis. Expansion of memory and effector T cells in vivo in transgenic mice constitutively expressing CD70 on T cells was limited in the presence of Fas-mediated T cell apoptosis. CD70 costimulation during the peak of influenza virus infection drove Fas-mediated apoptosis

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1290015

of influenza-specific $CD8^+$ T cells during the contraction phase and resulted in impaired memory responses to virus rechallenge. These findings reveal the roles that CD27/CD70 costimulation and Fas-mediated apoptosis play in shaping both primary and memory $CD8^+$ T cell responses.

HIV's Purinergic Surge



Macrophages have been known to serve as a reservoir for HIV-1 in infected individuals, but little is known about which macrophage proteins promote HIV replication. Hazleton et al. (p. 4488) have identified a role for purinergic receptors during HIV-1 infection of human macrophages. Treatment of primary human macrophages with oxidized ATP, which is known to inhibit the $P2X_7$, $P2X_1$, and $P2X_2$ purinergic receptors, significantly inhibited replication of several different HIV strains in a dose-dependent manner relative to untreated infected macrophages. Treatment with specific inhibitors of $P2X_1$, $P2X_7$, or $P2Y_2$ also caused a significant decrease in HIV replication, although HIV-1 entry was inhibited specifically by treatment with a $P2X_1$ antagonist. Intriguingly, binding of the HIV envelope protein gp120 to the macrophage cell surface triggered the release of extracellular ATP from macrophages. The authors proposed that this extracellular ATP binds to $P2X_1$ receptors and facilitates virus entry, whereas engagement of $P2X_7$ and $P2Y_2$ receptors promotes replication later in the viral life cycle. These results suggest that purinergic signaling may serve as a potential therapeutic target for inhibiting HIV replication in macrophages.

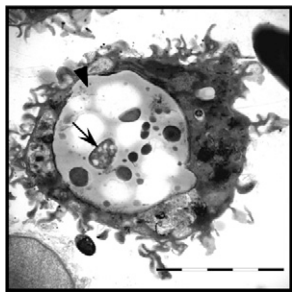
Innate Adaptation

Adaptive immune responses to chronic viral infections have been characterized in great depth, but the role of innate immunity is less clearly defined. Clingan et al. (p. 4432) assessed the nonredundant contributions of the RIG-I–like receptor (RLR) and nucleic acid-sensing TLR signaling pathways during acute or chronic lymphocytic choriomeningitis virus (LCMV) infections in mice. RLR signaling was important for optimal responses against acute infection, including type I IFN production, control of viral replication, and LCMV-specific $CD8^+$ T cell activation. In contrast, nucleic acid-sensing TLR signaling was needed for effective anti-LCMV Ab responses and control of chronic infection. Mice with a mutation affecting TLR3, -7, and -9 signaling had diminished Ab responses during both acute and chronic infection, with a strikingly larger reduction in chronic infection. This suggests that sustained engagement of nucleic-acid sensing TLRs may contribute to prolonged anti-LCMV Ab production. Overall, these data discern the different contributions of RLR and nucleic acid-sensing TLR signaling during chronic infection and suggest that innate immune responses have long term consequences for adaptive immunity.

Restraint through Diversity

The role of regulatory T cells (Tregs) in rheumatoid arthritis (RA) has been difficult to assess due to contradictory observations indicating that the frequency of Tregs is elevated within arthritic joints compared with healthy joints, yet their presence does not appear to be correlated with attenuated arthritis symptoms. Oh et al. (p. 4171) examined how TCR specificity contributes to the ability of Tregs to suppress RA symptoms in a mouse model of spontaneous autoimmune arthritis. Transgenic mice expressing an experimental autoantigen and a clonotypic TCR specific to this Ag developed arthritis spontaneously despite detection of Tregs specific for the experimental Ag. Transfer of polyclonal Tregs from mice with unmanipulated TCRs into prearthritic mice expressing the clonotyic TCR suppressed the development of arthritis. In contrast, transfer of Tregs expressing the clonotypic TCR did not mitigate arthritis development. Polyclonal Treg treatment appeared to suppress arthritis in part by inhibiting the accumulation of IL-17–producing $CD4^+$ T cells in joint-draining lymph nodes. Clonotypic TCR Tregs were able to suppress $CD4^+$ effector T cells with the same Ag specificity in vivo but did not prevent expansion of nonclonotypic TCR Th17 cells, nor did they exert any bystander suppression effects. Together these data support a role for varied TCR specificities among Tregs in the suppression of spontaneous autoimmune arthritis.

Molecular Assault on Mycobacteria



The neutrophil serine proteases cathepsin G (CG) and neutrophil elastase (NE) are critical for antimicrobial responses to multiple bacterial and fungal infections of the lung, but their effect on *M. tuberculosis* is not well understood. Steinwede et al. (p. 4476) examined how CG and NE affect lung immunity to mice infected with *M. tuberculosis* BCG. Clearance of *M. tuberculosis* BCG from the lungs was significantly compromised in CG-deficient and CG/NE-deficient mice, compared with wild-type (WT) mice. CG-deficient mice showed significant granuloma formation, which was even more extensive in CG/NE-deficient mice, relative to WT mice. Analysis of bronchoalveolar lavage from infected mice indicated that neutrophils were the predominant source of CG and NE at the site of infection. Infection of chimeric mice in which the hematopoietic system was deficient in CG and NE resulted in a greater mycobacterial load in the lungs relative to control mice. Interestingly, treatment of mice with liposome-encapsulated CG and NE reduced the mycobacterial lung burden and was most effective through repeated application. These observations characterize the antimycobacterial activity of CG and NE and support further investigation into their potential as a therapeutic treatment.

Summaries written by Christiana N. Fogg, Ph.D.